Fetal Therapy for Down Syndrome: Report of Three Cases and a Review of the Literature

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ABSTRACT:
Background: Down syndrome (trisomy 21) is a well-known cause of mental retardation. It can be diagnosed in early pregnancy. Scientists have made great strides in outlining the pathophysiologic mechanisms of mental retardation in Down syndrome. Much less has been published on human therapy. To our knowledge, these are the first published cases of fetal therapy for Down syndrome.
Methodology: Reports of three cases. In all cases, treatment was both biochemical (e.g. nutritional) and educational. In all cases, treatment was both before and after birth.
Results: All children lacked the characteristic faces usually seen in the children with Down syndrome. This suggests a treatment effect before birth. All children had better than expected development.
Discussion: Enhancement of development is proposed as a new therapeutic principle. Developing neurons exchange neurotrophic factors during development when they give or receive stimulation from other neurons. Neurons which receive neurotrophic stimulation survive, and those, which do not, are lost to apoptosis. The developmental therapeutic principle seeks to

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optimize brain development. Biochemical inputs (neurotransmitters, drugs, hormones, nutrients) and functional stimulation are integrated to optimize the growth and survival of neurons individually; other cells; subcellular organelles; and the brain as a whole. Treatment may be before and after birth, both biochemical and functional. These principles may be applied to Down syndrome, other conditions, and normal fetuses or children.
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The relative importance of biology (nature) and experience (nurture) in brain development has long been debated in science, medicine, and philosophy.

Over the years, ample evidence has accumulated to support key roles for both nature and nurturing. Therefore, if one assumes the point of view that both are important, effective therapeutic interventions aimed at enhancing brain development should be based on both biology and experience.

At the 69th AAPS meeting (2012), the "five-square" protocol was proposed for Down syndrome, other developmental disorders, and for normal children. This protocol should include biomedical treatments before and after birth; educational treatments before and after birth; and breastfeeding, which is both experiential and biochemical in nature.

Brain development could be viewed as a therapeutically modifiable process. This report will discuss several clinical cases that approximate the "five-square" treatment strategy in children with Down syndrome. Research with trisomic mouse models of Down syndrome has begun to elucidate how Down syndrome affects brain development. Recent results published in the literature show that, at least in treated mice, correcting the problems early in development can result in improved neurologic performance.

Case Reports

Case 1

This 39-year-old white G1P0 mother initiated all treatments on her own. She did not know the child had Down syndrome before birth and prenatally was trying to enhance brain development in general. She delivered a 2,806-g male infant at 40 weeks. The maternal serum screen revealed a 1 in 27 risk of Down syndrome. Amniocentesis was not done. APGAR scores were 9 and 10. The face did not appear to have canonical features associated with Down syndrome, but the karyotype was 47,XY,+21.

During pregnancy, the mother took a high-dose prenatal vitamin with docosahexanoic acid (DHA). Vitamins B1, B2, B6, and B12 dosages were at 10 to 20 times the recommended daily allowance (RDA). Most other nutrients were at dosages one to five times the RDA. She took a ginger-based candy three times daily and Gotu-Kola 950 mg twice daily. Gotu-Kola (Centella asiatica) is a parsley-like herb that inhibits

acetylcholinesterase, has antioxidant properties, and is thought to enhance memory, cognition, and mood.[1]

The child was nursed for 3 years. During breastfeeding, the mother discontinued Gotu Kola, added choline, and continued vitamins.

During pregnancy, the mother read aloud to the child 30 minutes per day. She worked in an environment where music was ubiquitous. The mother felt that the baby did not like certain songs because when those songs were played, the baby kicked so much that the mother had to move.

From birth to 8 months, the baby received a yoga-based passive movement stimulation program.[2] He also received a broad educational program in the style of Glen Doman and colleagues, starting at birth.[3,4,5,6] Reading flashcards began at 6 months. The mother read five to 15 books per day to her child. Counting on fingers and math flash cards began at 8 months. Counting was integrated in all aspects of daily life. Testing the baby was strictly avoided. Attachment parenting was practiced.[7,8,9,10] Consequently, the baby slept with his mother and received constant verbal and tactile stimulation from her. The baby slept prone at all times. The gross motor program was interrupted at the time of heart surgery at 6 months. Subsequently, gross motor development lagged, but later recovered.

Developmental achievements were normal or only mildly delayed. The evaluators said they "had never seen such a child with Down syndrome." He could read and respond with gestures by 19 months.[11] He could read aloud by 23 months.[12] By 25 months, the child read The Eye, a kindergarten-level Dr. Seuss book,[13] aloud from cover to cover. At 34 months, a developmental evaluation at an experienced developmental clinic included the Test of Early Language Development (TELD-3); the Clinical Evaluation of Language Fundamentals (CELF-Preschool-2); and the Battelle Developmental Inventory (BDI-2). Receptive and expressive speech met most milestones for three-year-olds and some for four-year-olds.

Case 2

This 43-year-old white G4P3 mother initiated all treatments on her own, and the authors only report them. She did not know the children had Down syndrome before birth and prenatally was trying to enhance brain development in general. She underwent Cesarean section at 36 weeks because of a worrisome fetal tracing. She delivered twin boys. At birth, the twins did not have the typical physical features of Down syndrome. A nurse noticed short ears on one boy. Blood chromosomes revealed that each twin had a karyotype of 47,XY,+21. The neonatal course was uncomplicated.

During pregnancy the mother took 1,200 mcg folate; a B-50 complex (50 mg of each B vitamin); vitamin C, 500 mg daily; and 600 mg niacinamide (vitamin B3) one to three times daily.

The infants were breastfed. At 8 months, one twin was engaged and engaging, while the second was immobile and had a "dull look in his eyes." Two days after starting 800 mcg folate daily, the formerly immobile twin crawled across the floor on his forearms. The twins were placed on a high-dose multivitamin at about 8-12 months.[14]

As prenatal education, the mother exposed her children in utero to classical music on a loud radio one hour daily. She also sang to them one hour each day.

Postnatally, the mother focused on teaching constantly, and rarely tested. The twins spent a lot of time on the floor crawling to stimulate gross motor development. Eye-hand and manual development were stimulated with an abacus. The twins were taught "signing exact English." This method supports verbal/spoken language.[15] They could respond to reading material by hand signing before they could communicate orally. Reading to the children began early. Counting began at 2-3 years of age. There was exposure to music, singing, and drumming. Physical development was supported from an early age. They learned to swim at one year. A basketball hoop was made to suit the stature of young children.

Both twins could read, write, and count to 100 by age 4. At this writing, the twins are 19 years old. They engage in a vigorous program of exercise two hours daily: they walk, play basketball, and lift weights. In the summer they swim daily. Both are avid readers, and they love to draw. One writes a lot, the other not so much. Each can lead group prayer (for example, a Roman Catholic rosary). They sing and drum daily. The twins took a standard home school program with adaptation up to the end of high school. They are not employed, but invest their energies mostly in athletics.

Case 3

This 38-year-old G2P1 mother approached us during pregnancy because of a high risk of Down syndrome. We had initiated discussion with an institutional review board (IRB) about submitting a specific and systematic treatment protocol for pregnancies and young children with Down syndrome. However, the IRB decided it would no longer work with small independent investigators, and a second IRB proved too expensive for a small private practice. Since treatment was limited to dietary supplements, and since the goal was innovative therapy rather than research, it was felt that the treatment was exempted from direct governance by the research ethics board.[16] Informed consent was given.

Maternal serum indicated a Down syndrome risk of one in five. Ultrasound revealed a short femur, increased nuchal thickness, and flat nasal bridge. The mother declined amniocentesis, and she delivered a 2,381-g female infant at 37 weeks, with normal APGARs. The examining geneticist stated that the baby did not have the typical physical features of a neonate with Down syndrome. The karyotype was 47,XX,+21.

Prenatal biomedical treatment consisted of a high-dose multivitamin (B vitamins at 25 to 100 times RDA). A similar high dose multivitamin was used postnatally (Nutrichem).

The mother read and sang to her unborn baby. The father also sang to the baby with his head in physical contact with the mother's abdomen. Music was also played.

The mother now reads and sings to the child. Grandmother sings in Spanish. The father presents reading flash cards, and reads prayers to the child.

The baby was crawling on the third day of life.[17] Evaluation by a regional developmental center at 9 months showed an overall developmental age of 7 months on the Early Learning Achievement Profile (ELAP).

Discussion

The chromosomal origin of Down syndrome was discovered by Gautier, Le Jeune, and Turpin.[18] That discovery lead to an understanding of Down syndrome as trisomy of chromosome 21. While accurate, it did not suggest a treatment. From the same era, Turkel[19] envisioned Down syndrome as a biochemical disease. If the whole chromosome was present in triplicate, then each gene was also in triplicate. Considering one gene at a time could reduce one large problem to many smaller ones.

The development of trisomic mouse models of Down syndrome enabled the study, analysis, and treatment of the disease, one gene at a time. Efficacy of treatment has been demonstrated in mouse models, especially when carried out early in development.

Classically, anatomy formed the basis for surgical treatment. Physiology and pharmacology formed the basis for medical treatment. Embryologic errors were known to cause developmental anomalies, but they did not form the basis of treatment. Genetic, congenital, or neurologic disorders were, in the past, thought to be untreatable. This is now changing. Developmental enhancement may be a new therapeutic principle, with novel properties.

Decades ago, it was noticed that nutrient deficiencies could cause birth defects. Correction of these deficiencies before conception prevented birth defects.[20,21] For the last several decades folic acid has been recommended clinically to prevent spina bifida.[22] Thus, treatments before conception are well known to affect outcomes months or years later.

In development, "timing is everything." The neural tube closes 28 days after conception. Taking folate before this time may prevent spina bifida; no amount of folate could undo the condition after delivery. Early in development, the effect of both beneficial and harmful influences is magnified. Later, benefits and harms diminish and become harder to detect.

Timing is even more important than specific treatment. Rapid cell division in early development leads to exponential expansion of cell number. One-carbon molecular fragments (mono-carbons) are needed for synthesis of purines, pyrimidines, DNA, RNA, proteins, neurotransmitters, and other molecules. Vitamins, such as folic acid and vitamin B12, and methyl donors, such as betaine and choline, support mono-carbon metabolism. Several of these (e.g. B12, folate, betaine) may prevent neural tube defects in early development.[23] Needed factors should be supplied before the developmental process begins. Benefits may last a long time—even a lifetime.

Studies by D.J. Barker and colleagues found that intrauterine factors, as reflected by birth weight and birth outcomes, influence adult diseases at ages 60-80.[24] Adult hypertension, heart disease, emphysema, and stroke were influenced by intrauterine factors acting six or seven decades earlier. Maternal undernutrition, as reflected by low

birthweight, may result in adult type 2 diabetes, hypertension, hyperlipidemia, and syndrome X.[25] Barker and colleagues dubbed this concept "fetal programming." From the work of Barker and others, one may conclude that development does not end at organogenesis, but continues through early life.

After organs have been formed, tissues, cells, subcellular organelles, and even molecular changes may occur. Treatment of inborn errors of metabolism could be viewed as epigenetic modification of development. If education depends on plastic modification of synapses, subtle development occurs at a more microscopic degree through much of life. Later adult diseases, seemingly remote from development, are nonetheless still influenced by developmental processes.

One of the most important aspects of development is neuro-embryology. At each step in brain development, an excess is elaborated, followed by pruning. Pruning by programmed cell death is apoptosis.[26] An excess of neurons, then dendrites, dendrite branches, dendritic terminal boutons, and synapses are elaborated, and then pruned. Neuron replication occurs mostly from 8-16 weeks.[26] Neurons migrate to their destinations from 18-25 weeks. Neurons then elaborate branching dendritic trees, form synaptic connections with other neurons, and project axons to targets. Glia and myelin develop. Neurons that give and receive stimulation "reward" each other with trophic molecules, and therefore they support their mutual survival. Neurons that do not communicate do not exchange trophic molecules, and therefore die by apoptosis.

Brain development, like organogenesis, was historically considered a "fait accompli." Experience dictates otherwise. Imagine brain development in three children. One grows up in a house where English is spoken. This child will be proficient in English. A second child, growing up in a house with three languages, will be proficient in all three. A third child, not exposed to any language up to the age of 10, will likely suffer permanent loss of faculties and learn only with great difficulty. Brain development is substantially modifiable.

Apoptosis—the programmed loss of brain cells—might seem harmful, but is in fact necessary for good brain function. One could imagine two brains. In the first, neurons A, B, and C are formed. For this example, A has better connections than B, which has better connections than C. In a second brain, replication of neurons is enhanced. Neurons AAA, BBB, and CCC are formed. After apoptosis, the best three survive. In the second brain, A, A, and A are left. The second brain has the same number of neurons, but higher quality neurons were selected. Improved brain function results from an interaction between enhanced replication with enhanced selection.[27,28] If poorly functioning and poorly connected neurons were lost preferentially, this would produce a neural network five times as effective at learning and problem-solving.[27,28]

Beginning in the early third trimester, neurons are rapidly lost due to apoptosis. Some early projection pathways provide wide-reaching stimulatory support to neurons throughout the brain until those neurons can make connections with other neurons. These pathways include the basal forebrain cholinergic neurons[29] and the adrenergic locus ceruleus neurons.[30] Maintaining or enhancing these pathways supports the neu-

rogenesis of many brain areas. Growth and survival of neurons depends on the dynamic interaction of replication and apoptosis.

One can now see how to modify the process of brain development for benefit or detriment. Children and/or animals subjected to sensory or functional deprivation suffer partial or temporary, to complete or permanent, loss of neurons, projection tracts, sensory, analytic, and/or motor capabilities. Children and/or animals given, singly or in any combination, increased sensory, motor, electrical, chemical, physiologic, or social stimulation develop and maintain greater neurologic capability and function. A neuron may be stimulated by functional sensory or motor input; by neurotransmitter or agonist input; or by reuptake inhibition of the neurotransmitter. The stimulatory effect of a drug on a target neuron could be functionally equivalent to sensory input. Since purely functional or educational approaches may be equivalent to drugs, their importance should not be minimized or neglected. Practically, brain mass and function can grow by use, just as a muscle grows from exercise.[3,4,5,6] Before reviewing treatments, the developmental perspective on studies must be considered.

Imagine a randomized controlled trial of growth hormone in middle-aged males. Such a trial could purport to prove growth hormone had no influence on height. That is because, by middle age, height is set at its final possibility. That possibility is partially genetic and partially environmental. The time period of plasticity for height likely begins during intrauterine life, but extends no further than a person's early 20s at the latest. Even if methodologically admirable, such a trial is developmentally misguided. The strength of developmental effects might approximate a plot of exponential decay. Such a curve would be steep at time near zero, but flattens out later. In the flat part of the curve, a very long duration of treatment is necessary to see a modest benefit, or it may be impossible to detect such a benefit. Trials of short duration, at advanced age (e.g. more than five years), could conclude that beneficial treatments are purportedly useless because they fail to account for the influence of developmental time.

Deficiencies of many vitamins cause decrements of neurologic function, which may be restored on repletion. These effects are numerous in animals across many species.[20,21] Many human neurologic diseases and neurotransmitter pathways are influenced by biochemistry and nutrition.[31,32] Experiments in normal children indicate beneficial effects of multiple micronutrients.[33] Nutritional support at developmentally important times should benefit brain development.

Some have advocated high-dose multivitamins in Down syndrome.[14,19,34,35] After Harrell's encouraging report,[35] six subsequent randomized controlled trials found no benefit of multivitamins.[14,36] In most of these trials there were insufficient numbers of patients and they may represent type II errors.[36] Most trials had no patients under age 5.[14,36] The treatments were of limited duration and were given late in development.[14,36] Since nutrient deficits have been documented in Down syndrome, MacLeod[14] and Ani et al.[36] conclude that these randomized trials lack credibility for these reasons. Eilander et al. reviewed micronutrient trials in normal children. Two trials at one year showed

clear benefits.[37] Trials in those older than 5 years had subtle benefits that required large numbers to show statistical significance. These results in normal children corroborate MacLeod and Ani et al.

Safety concerns about vitamins often represent erroneous or hyperbolic claims, from those who may lack training and experience in therapeutic nutrition, based on less than compelling data. High doses of vitamin C have been claimed to cause oxalate excretion, kidney stones, uricosuria, vitamin B12 deficiency, systemic conditioning, and pro-oxidant effects.[38] Careful and thorough reviews have found no evidence of harm other than osmotic diarrhea.[38] Vitamin E intakes well above the RDAs have consistently been shown to lack adverse effects.[38] Treatment of a wide variety of inborn errors of metabolism may be safely carried out with B vitamin doses as high as 10-1000 times RDA.[39] Higher doses of vitamins (100 times RDA for B vitamins) have been used safely in Down syndrome since the 1950s.[19] High-dose prenatal vitamins (10-100 times RDA) have been used safely without prescription for decades. It is unlikely such supplementation would have a harmful effect.[40]

Case reports have limitations but can demonstrate what is possible. The cases reported here suggest that Down syndrome patients might be capable, with a combined program of education and biomedical treatments before and after birth, of greater intellectual achievement than expected.

The recent development of mouse models of Down syndrome makes great progress possible. Most prominent is the Ts65Dn mouse. This model is trisomic for most of the genes found on human chromosome 21. Brain development in trisomic mouse models resembles human Down syndrome. They have similar physiologic, anatomic, and functional deficits. In mouse models, problems have been analyzed and elucidated, and treatments have been proven to be beneficial. Neurodevelopmental fetal therapies have been proven in mouse models. Selected prenatal or early postnatal treatments are considered here. Similar treatments given later in life often have less effect.

Environmental enrichment (including exercise) improves development in laboratory animals. Prenatal environmental stimulation of the mother results in improved neurologic performance of progeny after birth.[41] Anatomic studies of progeny demonstrated lasting increased thickness of the cerebral cortex and enhanced arborization of dendrites.[41] Perinatal exercise and environmental enrichment resulted in restored anatomy, memory, behavior, and learning.[42,43]

Basal forebrain cholinergic neurons (BFCNs) project widely throughout the brain. These neurons provide afferent trophic stimulation so that developing neurons will not be lost to apoptosis before they can connect with other neurons. Perinatal choline supplementation supports cholinergic transmission by the BFCNs.[29] Choline supports cognitive function; it is neuroprotective; it enhances neurotrophic function. Ts65Dn mice receiving choline during pregnancy and lactation had improved cognitive function as adults.[29] BCFNs are also sensitive to enhanced oxidative stress. Superoxide dismutase, a gene present on chromosome 21, converts superoxide (O2-) to hydroxyl radical.

Accumulation of excessive amounts of hydroxyl radical may cause oxidative stress. Perinatal treatment with tocopherol (vitamin E) protected basal forebrain cholinergic neurons from oxidative stress and restored anatomy, physiology, and behavioral and cognitive function.[44]

Patients with Down syndrome are often depressed and may improve with selective serotonin reuptake inhibitors. SSRIs enhance hippocampal neurogenesis in adults. Fluoxetine, a serotonin reuptake inhibitor, has been given to Ts65Dn mice, both in the early postnatal period and during pregnancy. Neurogenesis (as measured histologically) and behavioral performance were restored.[45]

The predominant stimulatory neurotransmitter of the brain is the amino acid glutamate. The predominant inhibitory neurotransmitter, opposing glutamate, is gamma amino butyric acid (GABA.) Blocking GABA, therefore, is stimulatory. In Down syndrome and in Ts65Dn mice, excess GABA-ergic stimulation, which has an inhibitory effect, may possibly explain a calm disposition. GABA blockade with pentylenetetrazole (PTZ) has been well known for decades. In animal experiments to study epilepsy, high-dose PTZ is used to permanently increase seizure frequency. As a result, the U.S. Food and Drug Administratiion (FDA) banned PTZ in the U.S. PTZ has a generalized stimulatory effect, stronger than caffeine, and it may be used in lower doses as a respiratory and/or cardiac stimulant under names such as metrazol or cardiozole. It is used this way outside the United States. In Ts65Dn mice, perinatal PTZ restored memory and cognitive function, and this effect persisted for 3 months after the drug was discontinued.[46] Hoffman La Roche has developed a "selective" GABA inhibitor, R04938581. Like PTZ, it fosters restoration of cognitive function.[47]

One gene on chromosome 21 is the dual-activity tyrosine (Y) phosphorylation regulatory kinase (DYRK1A) gene. This important gene has multiple influences in brain morphogenesis and synaptic plasticity. It regulates other genes and proteins in neurodevelopment. Transgenic mice with three copies display many features of Down syndrome. When the number of gene copies is reduced to two, normality is restored. In Ts65Dn mice, green tea extract (Epi-Gallo-Catechin Gallate/EGCG) blocked the harmful effects of DYRK1A and restored normal physiology, learning, and behavior.[48]

Conclusion

Neurogenesis (replication, survival, and organization of neurons) may be enhanced in many ways. Case reports suggest that several nutrients and drugs are promising. Experiments with mouse models may lead to effective treatments. Proper timing of treatment is crucial.

Better understanding of brain development could benefit all children, not just those with Down syndrome.

References

[1] Wattanathorn J, Mator L, Muchimapura S, et al. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of Centella asiatica. *J Ethnopharmacol* 2008;16(2):325-332. doi:10.1016/j.jep.2007.11.038.

[2] Sumar S. *Yoga for the Special Child: A Therapeutic Approach for Infants and Children with Down Syndrome, Cerebral Palsy, Learning Disabilities*. Sarasota, Fla.: Yoga for the Special Child; 1998.

[3] Doman GJ, Doman JJ. *How to Teach Your Baby to Read.* Garden City Park, N.Y.: Square One Publishers; 2006.

[4] Doman GJ, Doman JJ. *How to Teach Your Baby Math.* Garden City Park, N.Y.: Square One Publishers; 2006.

[5] Doman GJ, Doman D, Hagy B. *How to Teach Your Baby to Be Physically Superb.* Garden City Park, N.Y.: Square One Publishers; 2005.

[6] Doman, GJ. *What to Do about Your Brain-Injured Child.* Garden City Park, N.Y.: Square One Publishers; 2005.

[7] Sears W, Sears M. *The Attachment Parenting Book: A Commonsense Guide to Understanding and Nurturing Your Child.* Boston, Mass.: Little, Brown and Co.; 2001.

[8] Newton R. *The Attachment Connection: Parenting a Secure and Confident Child Using the Science of Attachment Theory.* Oakland, Calif.: New Harbinger Publications; 2008.

[9] Morrison K, Doman D. *Naturally Better Kids: Dramatically Improve Your Child's Life Naturally.* NBK Publishing; 2010.

[10] Macdonald J, Stoika P. *Play to Talk: a Practical Guide to Help Your Late-Talking Child Join the Conversation*. Madison, Wis.: Kiddo Publising; 2007.

[11] Sharing inspiration to support the Yamini Foundation. In: Durkin A. *Down Syndrome: a Day to Day Guide*. Available at: http://dsdaytoday.blogspot.com/2011/10/sharing-inspiration-to-support-yamini.html. Accessed Jan 14, 2014.

[12] Jett "reading" at 16 months. In: Durkin A. *Down Syndrome: a Day to Day Guide*. Available at: http://dsdaytoday.blogspot.com/2011/07/jett-reading-at-16-months.html. Accessed Feb 18, 2014.

[13] Teaching your baby or child to read. In: Durkin A. *Down Syndrome: a Day to Day Guide*. Available at: http://dsdaytoday.blogspot.com/2011/03/teaching-your-baby-to-read.html. Accessed Jan 14, 2014.

[14] MacLeod K. *Down Syndrome and Vitamin Therapy*. Ottawa, Canada: Kemanso Publishing; 2003.

[15] Gustason G, Zawolkow E. *Signing Exact English*. Los Alamitos, Calif.: Modern Signs Press; 1993.

[16] Eyadhy AA, Razack S. The ethics of using innovative therapies in the care of children. *Pediatr Child Health* 2008;13:181-184.

[17] Baby T Crawling_0002. Available at: http://www.youtube.com/watch?v=wIibpj1Mhiw. Accessed Jan 14, 2014.

[18] Lejeune J, Gautier M, Turpin R. Les chromosomes humains en culture de tissus. *C R Hebd Seances Acad Sci* 1959;248(4):602-603.

[19] Turkel H, Nusbaum I. *Medical Treatments of Down Syndrome and Genetic Diseases*. Southfield, Mich.: UBIOTICA; 1985.

[20] Combs Jr, GF. *The Vitamins: Fundamental Aspects in Nutrition and Health*. 2nd ed. San Diego, Calif.: Academic Press; 1998.

[21] Hurley L. *Developmental Nutrition*. Upper Saddle River, N.J.: Prentice Hall; 1980.

[22] Czeizel AE, Dudas I, Vereczkey A, Banhidy F. Folate deficiency and folic acid supplementation: the prevention of neural tube defects and congenital heart defects. *Nutrients* 2013; 51:4760-4775. doi:10.3390/nu5114760.

[23] Imbard A, Benoist JF, Blom HJ. Neural tube defects, folic acid and methylation. *Int J Environ Res Pub Health* 2013;10:4352-4389. doi:10.3390/ijerph10094352.

[24] Barker DJ. The origins of the developmental origins theory. *J Intern Med* 2007;261:412-417.

[25] Barker DJ, Hales CN, Fall CH, et al. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993;36:62-67.

[26] Volpe J. *Neurology of the Newborn*. Philadelphia, Pa: Saunders; 2008.

[27] Brown GD, Hulme C, Hyland PD, Mitchell IJ. Cell suicide in the developing nervous system: a functional neural network model. *Brain Res Cogn Brain Res* 1994;2(1):71-75.

[28] LeGrand EK. An adaptationist view of apoptosis. *Q Reb Biol* 1997;72(2):135-147.

[29] Moon J, Chen M, Gandhy SU, et al. Perinatal choline supplementation improves cognitive functioning and emotion regulation in the Ts65Dn mouse model of Down syndrome. *Behav Neurosci* 2010;124(3):346-361. doi:10.1037/a0019590.

[30] Salehi A, Faizi M, Colas D, et al. Restoration of norepinephrine-modulated contextual memory in a mouse model of Down syndrome. *Sci Transl Med* 2009;1(7):7ra17. doi:10.1126/scitranslmed.3000258.

[31] Melvyn R. *Nutritional Influences on Mental Illness*. 2nd ed. Tarzana, Calif.: Third Line Press; 1999.

[32] Lieberman HR, Kanarek RB, Prasad C. *Nutritional Neuroscience*. Boca Raton, Fla.: CRC Press; 2005.

[33] Jurg H. Vitamins and brain function. In: Lieberman HR, Kanarek RB, Prasad C, eds. *Nutritional Neuroscience*. Boca Raton, Fla.: CRC Press; 2005:207-233.

[34] Leichtman LG. Targeted nutritional intervention (TNI) in the treatment of children and adults with Down syndrome: principle behind its use, treatment protocols, and an expanded bibliography. In: Fish K, Fish Q, eds. *Down Syndrome: What You CAN Do.* Moodys, Okla.: Qadoshyah Fish; 2008: 93-112.

[35] Harrell RF, Capp RH, Davis DR, Peerless J, Ravitz LR. Can nutritional supplements help mentally retarded children? An exploratory study. *Journal Proc Natl Acad Sci* 1981;78:574-578.

[36] Ani C, Grantham-McGregor S, Muller D. Nutritional supplementation in Down syndrome: theoretical considerations and current status. *Dev Med Child Neurol* 2000;42: 207-213.

[37] Eilander A, Gera T, Sachdev HS, et al. Multiple micronutrient supplementation for improving cognitive performance in children: systematic review of randomized controlled trials. *Am J Clin Nutr* 2010;91(1):115-130. doi:10.3945/ajcn.2009.28376.

[38] Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr* 2005;81:736-745.

[39] Hillman RE. Megavitamin responsive aminoacidopathies. *Pediatr Clin North Am* 1976; 23:557-567.

[40] Nutrition Committee, Canadian Paediatric Society. Megavitamin and megamineral therapy in childhood. *CMAJ* 1990;143(10):1009-1013.

[41] Diamond MC. *Enriching Heredity: The Impact of the Environment on the Anatomy of the Brain*. New York, N.Y.: Free Press; 1988:84-105.

[42] Chakrabarti L, Scafidi J, Gallo V, Haydar TF. Environmental enrichment rescues postnatal neurogenesis defect in the male and female Ts65Dn mouse model of Down syndrome. *Dev Neurosci* 2011;33:428-441. doi:10.1159/000329423.

[43] Kida E, Rabe A, Walus M, Albertini G, Golabek AA. Long-term running alleviates some behavioral and molecular abnormalities in Down syndrome mouse model Ts65Dn. *Exp Neurol* 2013;240:178-89. doi:10.1016/j.expneurol.2012.11.022.

[44] Shichiri M, Yoshida Y, Ishida N, et al. α-Tocopherol suppresses lipid peroxidation and behavioral and cognitive impairments in the Ts65Dn mouse model of Down syndrome. *Free Radic Biol Med* 2011;50(12):1801-1811. doi:10.1016/j.freeradbiomed.2011.03.023.

[45] Bianchi P, Ciani E, Guidi S, et al. Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome. *J Neurosci* 2010;30(26):8769-8779. doi:10.1523/JNEUROSCI.0534-10.2010.

[46] Fernandez F, Morishita W, Zuniga E, et al. Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. *Nat Neurosci* 2007;10:411-413.

[47] Martinez-Cue C, Martinez P, Rueda N, et al. Reducing GABAA α5 receptor-mediated inhibition rescues functional and neuromorphological deficits in a mouse model of Down syndrome. *J Neurosci* 2013;33(9):3953-3966. doi:10.1523/JNEUROSCI.1203-12.2013.

[48] Guedj F, Sebrie C, Rivas I, et al. Green tea polyphenols rescue of brain defects induced by overexpression of DYRK1A. *PLoS ONE* 2009;4(2):e4606. doi:10.1371/journal.pone.0004606.